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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,345	01/18/2002	Yuen Kai Fung	D6087D	9974

7590 05/06/2004

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,345	FUNG ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 16-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-18-04.

Claims 1-27 are pending in the instant application.

Election/Restrictions

Claims 1-3 and 16-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 2-18-04.

Applicant's election without traverse of Group III, claims 4-15, in Paper No. 2-18-04 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 4 and 11, line 5, it is unclear what "amino acids 1-147" are referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 7-8, it is unclear what "amino acids 8-112" are referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 11-12, it is unclear what "an antisense construct complementary to the Gal-DBD-mx sequence" is referring to (e.g. is this an antisense complementary to the entire sequence?). Appropriate clarification is requested.

In claims 4 and 11, lines 13-14, it is unclear what "Gal-DBD which competes with the gal-BD-mx for the pGAL binding site" means. Appropriate clarification is requested.

In claims 4 and 11, line 16, it is unclear what "amino acids 1-147" are referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 17-18, it is unclear precisely what "the 130 amino acid C-terminus transactivation domain" is referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, line 19, it is unclear what "amino acids 350-439" are referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 21-22, it is unclear what "up to the first ATG" is precisely referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 23-24, it is unclear what "a 17-mer DNA-binding site for Gal4" is precisely referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, line 26, it is unclear what "TET-IN" is precisely referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, lines 28-30, it is unclear what "the first 80 bases of the TET-ON sequence including the ATG under the control of the pCMV promoter" is precisely

referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

In claims 4 and 11, line 32, it is unclear what "amino acids 1-207" is referring to (e.g. indicating an appropriate and corresponding SEQ ID NO. would be remedial).

This application does not comply with the *rules for the deposit of biological material as set forth below in the Suggestion for Deposit of Biological Material. For ATCC deposits*, please be sure to use the current address in Virginia, rather than the former address in Maryland.

The following is a quotation of the first paragraph of 35 USC § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and us the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 USC § 112, first paragraph as failing to provide an enabling disclosure for the claimed invention.

Claims 4-15 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Features and steps critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

It is apparent that the vectors pRIBS-X and pRIPS-X are required to practice the claimed invention. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC § 112, first paragraph, may be satisfied by a deposit of the vectors pRIBS-X and pRIPS-X. A suggestion for deposit of biological materials is provided:

The vectors pRIBS-X and pRIPS-X are required material for the compositions and treatment methods claimed , all of which are claimed in the instant invention. The specification does not provide a repeatable method for obtaining the vectors pRIBS-X and pRIPS-X, and it does not appear to be a readily available material. Deposit of the vectors pRIBS-X and pRIPS-X would satisfy the enablement requirements of 35 USC § 112 for the compositions claimed. A suggestion for deposit of biological materials is provided:

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Se 37 CFR 1.801 through 1.809. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent.

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to tone determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122. 6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer.

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine of imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereof.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and

that all restrictions on the availability to the public of the material so deposited will be irrevocable removed upon the granting of a patent.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of the vectors pRIBS-X and pRIPS-X to cells in vitro, does not reasonably provide enablement for an treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods comprising the treatment of local and metastatic breast and ovarian or prostate cancer comprising the administration of pRIBS-X or pRIPS-X, respectively. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery is highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

The nature of the invention. Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered therapy *per se*, delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are for the most part based on the ability to deliver exogenous genes in functional form to cells or tissues of interest.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the art of gene delivery is highly unpredictable. Crystal, in discussing the art of gene therapy, describes the "ideal gene transfer vector" to have among its attributes the ability to efficiently transfer genes and be specific for its target. Crystal furthermore teaches that the disadvantages of gene therapy or delivery include general inefficiency at achieving successful gene transfer as well as a general lack of available data regarding repetitive administration of DNA to whole organisms (page 405, second paragraph). Another major obstacle for *in vivo* delivery is to ensure delivery of the bioactive agent in sufficiently high numbers to appropriate target cells to be effective when administered *in vivo*. The delivery of genes to adequate numbers of target cells, for instance, and/or ensuring sufficient and appropriate gene expression in those cells are major difficulties for gene therapy methods (i.e. see Crystal on page 409, center column). The same is true for the instant invention comprising inducible gene transfer vehicles for gene delivery. The specification as filed teaches that the ability to tightly control tetracycline induced expression *in vivo* is difficult due to tissue heterogeneity and that generally the

pharmacokinetics of tetracycline varies within individual organisms as well as within tissues of a given individual (pages 36 and 41 of the specification).

A further difficulty in gene delivery is the unpredictable nature of gene therapy when one tries to extrapolate from animal models to human systems. Long lists of clinical trials exist which have yet to yield therapeutic benefits. Crystal points out that "no human disease has been cured by human gene transfer and it is not clear when this will be accomplished" (page 407, first column). Schofield *et al* teach advantages of various methods of *in vivo* delivery of genes, while also stressing that many of the details regarding cell targeting, cell entry and gene expression in target cells remain highly speculative. Furthermore, Schofield *et al* caution that *significant variations exist between animals*, and state that only limited conclusions could be drawn from animal studies which may be applied to the treatment of humans (pages 61-64). Verma *et al* teach the problems of gene delivery in whole organisms using non-viral vector approaches, using various delivery agents, and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teaches that non-viral gene transfer is much less efficient than virus-mediated transfer (page 100, last paragraph-page 101, first paragraph), while, according to Friedmann, the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of

in vivo inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke).

While these references acknowledge the usefulness of gene therapy and gene delivery using recombinant viral and non-viral vectors and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful therapy which current methods still must overcome, including the added limitations of utilizing inducible vectors whereby the appropriate delivery of antibiotics, heat or light is also highly unpredictable. As such, the disclosed utilities of the present specification which are drawn to a method of achieving sustained gene expression comprising the administration of a vector containing a heat or light inducible promoter in combination with tetracycline derived repressor and promoter elements are credible. The present rejection, therefore, is not for lack of utility, but rather for lack of enablement for the scope of the methods claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method treating breast, ovarian or prostate cancer and metastases thereof comprising the administration of any therapeutic genes subcloned into the vectors pRIBS-X and pRIPS-X. The specification teaches the *in vitro* expression of p53 in target cells *in vitro* following the administration of the pDATH vector comprising the heat shock promoter-tetp and further comprising the administration of doxorubicin and light, whereby p53 expression is sustained (i.e. as illustrated in Figure 8). The specification fails to teach the *in vivo* administration or treatment effects

provided for the instant compositions comprising the vectors pRIBS-X and pRIPS-X and further comprising a therapeutic gene subcloned into these vectors.

The breadth of the claims and the quantity of experimentation required.

The breadth of the claims is very broad. The claims are drawn to compositions and methods comprising the treatment of local and metastatic breast and ovarian or prostate cancer comprising the administration of pRIBS-X or pRIPS-X, respectively. In order to practice the invention over the scope claimed, it would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to the treatment of breast, ovarian or prostate cancer and metastases thereof in any organism comprising the administration of the recombinant vectors pRIBS-X and pRIPS-X, such that a subcloned therapeutic gene is delivered to appropriate target cells, the therapeutic gene is appropriately expressed, or in the case of antisense, the target gene is appropriately inhibited, and further that sustained expression of the delivered gene is obtained and whereby treatment effects are provided. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites for the appropriate target cells, modes of delivery and formulations to target appropriate cells and/or tissues whereby an appropriate therapeutic gene is delivered and further whereby sustained expression of the gene is obtained upon proper administration of the vectors claimed and treatment effects are provided. Since the specification fails to provide any particular guidance for the successful delivery of any therapeutic genes which have been subcloned into pRIBS-X and pRIPS-X vectors, whereby they are administered appropriately and

treatment effects provided in an organism, and since determination of these factors for a particular vector comprising a particular therapeutic gene is highly unpredictable for a particular organism, it would require undue experimentation to practice the invention over the scope claimed.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
4-29-04

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER